REMARKS

Present Status of the Application

Claims 58-60 were rejected under 35 U.S.C. 112, 2nd paragraph. Under 35 U.S.C. 103(a), claims 1-4, 11-18, 20, 38, 48, 50 & 58-60 were rejected as being unpatentable over Arcone et al. (1999 Biochimica et Biophysica Acta 1451: 173-) in view of Morrison et al. (2001 Current Opinion in Chemical Biology 5: 304-) and current practice in protein design as evidenced by Wells (1990 Biochemistry 29(37): 8509-), claims 39, 42-43 & 45-46 rejected over Arcone et al. in view of Morrison et al., current practice in protein design (Wells) and Veronese (2001 Biomaterials 22: 405-), and claim 47 rejected over Arcone et al. in view of Morrison et al., current practice in protein design (Wells), Veronese and Roberts et al. (2002 Advanced Drug Delivery Reviews 54: 459-).

In response, Applicants have amended claims 58-60 to overcome the 112 rejection, and have submitted the following remarks for the 103(a) rejections. Reconsideration of claims 1-4, 11-18, 20, 38-39, 42-43, 45-48, 50 & 58-60 is requested.

Discussion of the Rejection under 35 U.S.C. 112

For the 112 rejection, Applicants explain that the thrombin derivative in claims 58-60 does comprise SEQ ID NO:2, but SEQ ID NO:2 also includes the A chain at positions 1-49 thereof, and the positions 205 and 43 recited in claims 58/59/60 are positions of the B chain according to the base claim 1/2/20 ("...***the B chain*** *is substituted such that serine at position 205* ***thereof*** *is ... and histidine at position 43* ***thereof*** ..."), so that serine/ histidine at position 205/43 (of the B chain) recited in claims 58, 59 & 60 corresponds to serine/histidine at position 254 (=205+49)/92 (=43+49) in SEQ ID NO:2.

Nevertheless, for more clarity, Applicants still insert the phrase "*of the B chain*" after the terms "*position 205*" and "*position 43*" in claims 58-60 respectively. Such amendment should constitute no new issue requiring further search.

Discussion of the Rejection under 35 U.S.C. 103(a)

Examiner asserted that the effects of amino acid substitutions are cumulative by citing Wells, but Wells only shows that the effects of amino acid substitutions are well cumulative in the specific protein Subtilisin BPN' (S221A, H63A and D32A, see p. 8515, col. 2, 2nd paragraph). One of ordinary skill in the art well understands that whether the effects of amino acid substitutions are cumulative or not depends on the protein to be mutated. As indicated in the conclusion of Wells, there are certain exceptional cases for the cumulative effect (additivity) of mutants.

Thrombin is just a case where the cumulative effect (additivity) of mutants is absent, as shown in the Examples described in the specification. Furthermore, Inventors found only the combination of positions 43 and 205 was effective whereas other combinations of substitutions disclosed in Arcone, such as 203A205G (Example 2), 203A205A99N (Example 5), 205A99N (Example 10) and 203A205A (Example 11), were not effective. It was never easy to find specific effective combinations. For example, H43M disclosed in Arcone still maintains thrombin activity, but S205A or G203A did not show detectable activity (Table 1). Accordingly, in view of Arcone and Wells, one of ordinary skill in the art naturally would have selected the combination of positions 205 and 203, rather than the combination of positions 43 and 205 as recited in the claims of this invention. Thus, the effect of the claims of this invention is unexpected and non-obvious to the prior art.

In the case of *Procter & Gamble Co. c. Teva Pharmaceuticals USA, Inc., 566 F.3d 989 (Fed. Cir. 2009)*, the Federal Circuit noted in dicta that even if a *prima facie* case of obviousness had been established, sufficient evidence of unexpected results was introduced to rebut such a showing.

Moreover, according to the case of *Sanofi-Synthelabo v. Apotex, inc., 550 F.3d 1075 (Fed. Cir. 2008)*, a claimed isolated stereoisomer would not have been obvious where the claimed stereoisomer exhibits unexpectedly strong therapeutic advantages over the prior art racemic mixture without the correspondingly expected toxicity, and the resulting properties of the

enantiomers separated from the racemic mixture were unpredictable.

In addition, as mentioned in Applicants' last Response, Morrison et al. simply teach a general method of studying the importance of a non-alanine amino acid by substituting the amino acid with alanine (see the Abstract), and either can not show an effect of combining the mutations at S205 and H43. The other references cited for rejecting some dependent claims, Veronese and Roberts et al., also fail to teach the above feature of the independent claims 1, 2 & 20.

For at least the above reasons, claims 1-2 & 20 and claims 3-4, 11-18, 38-39, 42-43, 45-48, 50 & 58-60 dependent therefrom all patently define over the prior art.

CONCLUSION

For at least the foregoing reasons, it is believed that pending claims 1-4, 11-18, 20, 38-39, 42-43, 45-48, 50 & 58-60 of the present application are in proper condition for allowance. Rejoining of withdrawn claims 5, 21-36, 40-41, 44, 49 & 51-57 all dependent from claim 1 is also requested if Examiner would allow claims 1-4, 11-18, 20, 38-39, 42-43, 45-48, 50 & 58-60. If Examiner believes that a telephone conference would expedite the examination of the above-identified patent application, the Examiner is invited to call the undersigned.

Respectfully submitted,
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